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## **ESMO Minimum Clinical Recommendations for diagnosis, adjuvant treatment and follow-up of primary breast cancer**

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# ESMO Minimum Clinical Recommendations for diagnosis, adjuvant treatment and follow-up of primary breast cancer

## Incidence

- The crude incidence of breast cancer in the European Union is 109.9/100 000 females per year, the mortality 38.4/100 000 females per year, however with marked geographical variation.

## Diagnosis

- The diagnosis is based on clinical palpation, bilateral mammography and ultrasound. Pathologic diagnosis with fine needle aspiration or core needle biopsy should be obtained prior to any surgical procedure. Final pathological diagnosis should be made according to the World Health Organisation classification and the TNM (2002) staging system analyzing all tissue removed.

## Staging and risk assessment

- TNM-staging based on H&E staining, standardized grading, description of histologic type, and of resection margins should be reported. Determination of estrogen receptor (ER) and progesterone receptor (PR) status is mandatory, preferably by immunohistochemistry [III, B]. Reports of immunohistochemical results for ER and PR should include the percentage of ER- and PR-positive cells. When available, immunohistochemical determination of HER2 receptor expression should be performed at the same time. When semi-quantitative results of immunohistochemistry are ambiguous (+ +), *in situ* hybridization (FISH or CISH) to determine HER2 gene amplification should be considered.
- Routine staging examinations include physical examination, full blood counts, routine chemistry including liver enzymes, alkaline phosphatase, calcium; assessment of menopausal status.
- In patients with higher risk (N2 with  $\geq 4$  pos. axillary nodes, or T4 tumors, or with laboratory signs or clinical signs or symptoms suspicious for the presence of metastases), chest X-ray, abdominal ultrasound and isotopic bone scan are appropriate [III, B].
- Explore the possibility of hereditary cancer and evaluate adequate counselling of relatives [IV, D]. For node negative patients the following risk stratification to guide adjuvant treatment is recommended [III, B]. Even tumors smaller than 1 cm can benefit from adjuvant treatment with chemotherapy and/or tamoxifen [II, B]. See Table 1.

## Treatment plan

- Multidisciplinary treatment planning should be used to integrate local and systemic therapies as well as their sequence [III, B].

### Local therapy

#### *Invasive carcinoma*

- Generally, operable breast cancer is initially treated by surgery, using breast conserving surgery or mastectomy, both in combination with axillary dissection. Contraindications to breast-conserving surgery include multicentric tumors, large tumors (larger than 3–4 cm), tumor-involved margins after resection. The technique of sentinel lymph node biopsy may be used in centers with documented experience and accuracy. Breast radiotherapy is strongly recommended after breast conserving surgery [I, A]. Post-mastectomy radiotherapy has been recommended for patients with four or more positive axillary nodes [II, B] and is suggested for T3 tumors with positive axillary nodes [III, B].

#### *Ductal carcinoma in situ (DCIS)*

- When DCIS is treated by breast conserving surgery, all subgroups of patients benefit from adjuvant radiation as well as from adjuvant tamoxifen [I, B]. Adjuvant tamoxifen for DCIS reduces the recurrence rate of *in situ* and of invasive breast cancer.

### *Primary systemic therapy*

- Primary systemic therapy is indicated for inoperable locally advanced breast cancer (stage IIIB: T4, N2-3, regional M1) [III, B]. If possible it should be followed by both surgery and radiotherapy and postoperative systemic treatment. Primary systemic therapy is an alternative for large operable breast cancer, to allow breast conserving surgery [I, A].

### *Adjuvant systemic therapy*

- Before deciding whether to use adjuvant systemic therapy, the prognosis without adjuvant therapy should be estimated. For each individual, the choice of adjuvant therapy must take into account the potential benefits, possible side effects, and patient preference.

**Table 1.**

	Tumor size ER/PR <sup>a</sup>		Grading Age <sup>b</sup>		Comment
Low risk	<2 cm	positive	1	≥35	All factors must be present
Higher risk	≥2 cm	negative	2–3	<35	At least one factor present

<sup>a</sup>Using immunohistochemistry, ER/PR is usually considered positive, when ≥10% of cells are positive (weakly or strongly) for either ER or PR [IV, B]. Some endocrine responsiveness seems to remain even when only 1–10% of tumor cells are ER weakly positive [III, B]. ER and/or PR positive patients are considered “endocrine responsive”.

<sup>b</sup>No exact age threshold has been defined.

### Tamoxifen

- Patients with ER and/or PR positive tumors should receive tamoxifen 20 mg/d for 5 years [I, A]. Patients with ER and PR negative tumors [I, A] and/or HER2-positive tumors [II, C] should not receive it. Tamoxifen should be started when chemotherapy is completed [II, A]. Concurrent use of tamoxifen with radiation therapy is not recommended due to potentially increased risk of lung toxicity [III, C].

### Aromatase inhibitors

- The use of aromatase inhibitors instead of or in sequence with tamoxifen significantly reduces the risk of recurrence compared with tamoxifen, but no survival benefit has been demonstrated so far [I, A]. Furthermore, the absolute difference in recurrence-free survival is <5%. The long-term cardiovascular and skeletal adverse effects associated with aromatase inhibitors are an issue of concern. Certain subgroups (ER-positive/PR-negative, HER2-positive) seem to have a more marked benefit by the use of an aromatase inhibitor [III, C].

### Ovarian ablation

- Ablation of ovarian function is an alternative to CMF-based regimens for premenopausal patients with endocrine responsive tumors [I, A]. Bilateral ovariectomy and irradiation of the ovaries lead to irreversible ablation of ovarian function. LHRH analogs generally lead to reversible ovarian suppression. They should be given for at least 2 years [III, D].

### Chemotherapy

- Adjuvant chemotherapy should use a combination regimen, as shown in Table 2 [I, A]. In node-positive and node-negative disease anthracycline-containing therapy has been shown to be slightly superior in efficacy to intravenous CMF [I, A]. However, there seems to be a threshold dose for adjuvant anthracyclines, below which efficacy becomes inferior [I, A]. 4 cycles of AC have been shown to be comparable in efficacy to 6 cycles of CMF [I, A]. At the St Gallen consensus conference 2003 4 cycles of AC or 6 cycles of CMF were considered adequate treatment for ER and/or PR positive patients, while ER and PR negative tumors were

considered candidates for more prolonged chemotherapy. Adding 4 cycles of paclitaxel to 4 cycles of AC improves outcome in node-positive patients [I, A]. It is possible that other more intensive anthracycline- and/or taxane containing regimens are equally effective. Encouraging results have been described with dose-dense therapy using hematopoietic growth factors in addition to AC and taxanes. This approach is not considered standard at the present time.

## Follow-up

- History taking, eliciting of symptoms and physical examination every 3–6 months for 3 years, every 6–12 months for 3 years, then annually [A], with attention paid to long-term side effects, e.g. osteoporosis.
- Ipsilateral (after breast conserving surgery) and contralateral mammography every 1–2 years [D].
- Not routinely recommended for asymptomatic patients: blood counts, chemistry, chest X-ray, bone scan, liver ultrasound, CT-scans of chest and abdomen, and any tumor markers such as CA 15–3 or CEA [I, A].

## Note

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology

**Table 2.**

Node Negative (N0) Patient	
Low risk, endocrine responsive	Tamoxifen <b>OR</b> Nil
Higher risk, endocrine responsive:	
- Premenopausal	Chemotherapy, ovarian ablation → tamoxifen <b>OR</b> Chemotherapy → tamoxifen <b>OR</b> Ovarian ablation
- Postmenopausal	Tamoxifen* <b>OR</b> Chemotherapy → tamoxifen
Higher risk, endocrine non-responsive:	
- Premenopausal	Chemotherapy
- Postmenopausal	Chemotherapy
Node Positive (N+) Patient	
Endocrine responsive:	
- Premenopausal	Chemotherapy → tamoxifen ± ovarian ablation
- Postmenopausal	Chemotherapy → tamoxifen* <b>OR</b> Tamoxifen*
Endocrine non-responsive:	
- Premenopausal	Chemotherapy
- Postmenopausal	Chemotherapy

\*In postmenopausal patients, aromatase inhibitors (anastrozole, letrozole, exemestane) are an alternative.

are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

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